13. (Amended) The composition of matter according to Claim 12 wherein said central linker is selected [form] from the group consisting of a oligoglycine [or] and oligoalanine.

REMARKS

The remainder of this Amendment is set forth under the appropriate subheadings for the convenience of the Examiner.

Amendments to the Specification

The specification has been amended to correct obvious clerical errors and to meet the requirements of 37 C.F.R. § 1.825.

Amendments made to peptide sequences on page 7, line 32 are supported by the examples of suitable peptide sequences listed on page 22, lines 12-15.

Incorporation by Reference of Essential Material

Methods for chemically modifying amino acids by electrophilic substitution, nucleophilic substitution, activation reactions and addition reactions are generally known in the art and, therefore, are non-essential to the present application (see page 5, at lines 32-35 of the specification). Thus, Applicants have not incorporated essential material.

Because Applicants disclose a method for manufacturing SAMs in Example 1 on p. 22-23 of the specification, methods for manufacturing SAMs previously known in the art are also non-essential to the present application (see page 13, paragraph 1 to page 14, line 24 of the specification).

Claim Amendments

Claim 6 has been amended to more clearly define the scope of the claimed composition, particularly with regard to which types of presenting groups fall within the scope of the claim. Support for this amendment can be found on page 7, lines 1-6 and 17-20 and page 9, lines 19-32.

Claims 9, 11 and 13 have been amended to recite traditional language for Markush groups.

Claim 11 has also been amended to indicate that aspartic acid and glutamic acid are also suitable terminal amino acids. Support for this amendment can be found on p. 5 at lines 21-23 of the specification.

Restriction Requirement

During a telephone conversation on July 6, 1998 between Edgar W. Harlan, Jr., Agent for Applicants, and Examiner Achutamurthy, a provisional election was made with traverse to prosecute the claims of Group I (Claims 1-19). It was agreed that if claims of the elected group become allowable, the Examiner will reconsider the restriction requirement with a view to join the method claims of Groups II and III (Claims 20 and 21). Applicants affirm the election of Group I and reserve the right to file a divisional application or to take such other appropriate action as deemed necessary to protect the inventions of Groups II and III. Hence, Applicants do not hereby abandon or waive any rights in the Groups II and III inventions.

Sequence Listing

In response to the Notice to Comply with Sequence Rules 37 C.F.R. 1.821-1.825, a sequence listing has been submitted herewith.

Applicants' Invention

Applicants' claimed invention is directed to a composition of matter comprising a self-assembled monolayer (hereinafter "SAM") of peptides assembled on a solid support in a predetermined pattern and methods of making the same. The peptides used in the method comprise three regions: 1) a terminal amino acid that is bound directly to the solid support through its side chain, amino group or carboxy group designated the "terminal reactive group" (see p. 3, lines 1-5 and p. 5, lines 12-17 of the specification); 2) a group that will bind to one or more targets designated the "presenting group" (see p. 6, lines 28-30 of the specification); and 3) a peptide having an amino acid sequence selected to optimize a beta strand configuration and which is bound to the terminal reactive group and the presenting group and is designated the "central linker" (see p. 6, lines 6-11 of the specification).

Rejection of Claims 6, 9, 11 and 13 Under 35 U.S.C. § 112, Second Paragraph

The Examiner states that the term "presenting group" in Claim 6 is vague and indefinite.

Applicants have amended Claim 6 to more particularly define the scope of the subject matter defined by the term "presenting group."

The Examiner points out that Claims 9, 11 and 13 recite improper Markush groups. Applicants have amended Claims 9, 11 and 13 to adopt the language suggested by the Examiner.

Rejection of Claims 1-17 Under 35 U.S.C. § 102(a) Over Wang *et al.*

The Examiner states that Wang *et al.*, *Chem. Abstracts*, *125*:20, abstract no. 257089b, (1996) (hereinafter "Wang *et al.*") teaches peptide monolayers formed on a substrate which are of the recited type.

Wang *et al.* disclose a homogeneous monolayer of a molecular species which has a first terminal reactive group (i.e., a thiol group); a presenting group which can bind to a biological target (i.e., a peptide sequence which can bind to a cell); and an ethylene central linker which is bound to the amine group of the peptide and to the thiol (see Wang *et al.*, lines 12-13 and peptide formulas at line 15). None of the peptide monolayers taught by Wang *et al.* are deposited in a predetermined pattern.

Applicants claim a monolayer of peptides assembled on a solid support in a predetermined pattern (see Claims 1-16 of the subject application). The following statement on page 12, lines 13-20 of the specification makes clear that a feature of the invention is that the peptides are distributed on a surface in a specific pattern and are not distributed randomly or homogeneously:

> The terms "printed", "patterned" or "predetermined pattern" are defined herein to mean that the solid support has ordered areas where the peptides are bonded and not bonded to the solid support. That is, a printed or patterned solid support is expressly not intended to include a support with random or substantially homogeneous distribution of the peptide over its entire surface(s).

The peptide monolayers disclosed by Wang *et al.* are not deposited in a predetermined pattern, nor do Wang *et al.* teach or suggest how to form a monolayer of peptides on a surface in a predetermined pattern. Therefore, Claims 1-16 are novel over Wang *et al.*

In addition, the peptide monolayer disclosed by Wang *et al.* is linked to the solid support through an ethylene linker. Applicants' peptide monolayer is attached to the solid support directly by an amino acid side-chain, amino group or carboxy group of the terminal amino acid (see p. 3, lines 1-5 and p. 5, lines 12-17 of the specification). Therefore, the self-assembled monolayer claimed in Claim 17 is also novel over Wang *et al.*

Applicants peptide monolayers claimed in Claims 1-17 are novel over Wang *et al.* because, as claimed, they contain one or more elements not found in Wang *et al.* Therefore, Applicants respectfully request that the rejection be withdrawn.

Inventorship of Claims

Applicants confirm that the subject matter of Claims 1-21 was jointly invented by Applicants.

Rejection of Claims 19 and 20 Under 35 U.S.C. § 103(a) Over Wang *et al.* in View of Kumar *et al.*

Claim 20 is drawn to a non-elected invention which has been withdrawn from consideration in this amendment. Applicants note that the Examiner has not stated a specific rejection of Claim 18, but the claim has not been allowed. Both Claims 18 and 19, drawn to methods of manufacturing peptide SAMs having a predetermined patten, and Claim 20, drawn to a method of cell culture, are non-obvious over Wang *et al.* in view of Kumar *et al.*

The Examiner states that "Wang *et al.* teach a substrate comprising self assembled monolayers of peptides," and that "[t]he difference between Wang *et al.* and the instant claims is that the reference fails to teach the formation of the monolayers by using a stamp having a predetermined pattern on a substrate and forming the monolayers by a microstamping technique."

The Examiner summarizes the teachings of Kumar *et al.* as ". . . a method for the formation of monolayer assembled on solid surfaces using a microstamping techniques. . ." with ". . . a variety of molecular species that can be bonded onto a variety of solid supports . . . . among the molecular species those contributing or comprising peptide amide linkages are taught."

The Examiner states that because Kumar *et al.* teach that their microstamping method can be used to attach a variety of molecular species to a solid substrate, this provides a motivation to combine the reference with Wang *et al.* The Examiner concludes that it would have been obvious to one having ordinary skill in the art at the time of invention to have obtained self-assembled peptide monolayers as taught by Wang *et al.* using a microstamping technique to form the monolayers as suggested by Kumar *et al.*

Kumar *et al.* disclose a method of assembling a monolayer of a molecular species that has a first terminal functional group that can bind to the solid support; a spacer connected to the terminal functional group; and optionally a second functional group attached to the spacer that can bind to biological or chemical species (see Kumar *et al.*, Col. 10, lines 23-29). Kumar *et al.* teach that the spacer is a group that does not disrupt the packing of the SAM. The examples which Kumar *et al.* list as suitable spacers are saturated or unsaturated, linear or branched alkyl, aryl, hydrocarbons and their halogenated equivalents (see Kumar *et al.*, Col. 12, paragraph 1). Kumar *et al.* does not suggest that peptides could be used as spacers.

In addition, Kumar *et al.* disclose a method of assembling the molecular species on a solid support in a pattern which involves transferring to a stamp that has a predetermined pattern a solution of the molecular species. A solid support that can bind to the first functional group is then contacted with the stamp for sufficient time to allow the molecular species to bind to the solid support in the predetermined pattern (see Kumar *et al.*, Col. 15, paragraph 2). Kumar *et al.* also teach that a solid support which does not bind the first functional group can be coated with a thin film that will bind the first functional group (see Kumar *et al.*, Col. 14, paragraph 4). Kumar *et al.* do not teach or suggest that a coating material can be applied in a predetermined pattern.

Applicants' peptide molecular species used in the method of Claims 18, 19 and 20 form SAMs by binding directly to a solid support or to a compound deposited on a solid support by a side chain, amino group or carboxylic acid group of a terminal amino acid (see page 3, lines 1-5 and page 5, lines 15-20).

Applicants disclose two methods of patterning the peptide monolayers. In the first method, a solid support which will not bind the peptide is coated in a predetermined pattern with a compound that will bind the terminal reactive group of the peptide. The compound is deposited on the solid support in a predetermined pattern using a stamp. Then the solid support is

contacted with a solution of the peptide which then binds to the compound in the predetermined pattern. (See p. 15 at line 29 to p. 16 at line 6, Example 1 on p. 22-23, and Claim 18.)

In the second method, the solid support itself can bind the terminal reactive group of the peptide. In this method, a stamp is used to deposit a peptide solution directly onto the solid support in a predetermined pattern. (See p. 14, lines 25-33 and Claim 19.)

Neither Kumar *et al.* nor Wang *et al.* teach or suggest Applicants' method of forming a SAM in a predetermined pattern claimed in Claim 18 and exemplified on p. 22-23 of the specification. In Kumar *et al.*, the molecular species is applied with a stamp that has a predetermined pattern. In the method of Claim 18, a compound which can bind the molecular species is deposited on a solid support in a predetermined pattern using a stamp. Then a solution of the molecular species is brought into contact with the solid support. Kumar *et al.* do not teach or suggest that a compound other than the molecular species can be applied with a stamp in a predetermined pattern to obtain a SAM having a predetermined pattern. Wang *et al.* do not remedy the deficiencies of Kumar *et al.* because Wang *et al.* form homogeneous membranes with no predetermined pattern. Therefore, the method of Claim 18 is novel and non-obvious over Wang *et al.* in view of Kumar *et al.*

In addition, Applicants' use of a peptide molecular species has several advantages over the molecular species used by Wang *et al.* and Kumar *et al.* Because Applicants' peptide molecular species is attached directly to the solid support, it can be synthesize by standard solid phase peptide synthesis protocols in high purity and used directly to form a SAM. The molecular species disclosed by both Wang *et al.* and Kumar *et al.* have alkyl or aryl spacers which are added to the peptide by additional synthetic steps (see Wang *et al.*, lines 12 and 13).

In addition, Applicants' peptide molecular species can assemble into a closely packed, ordered monolayer such as a β-sheets structure which relies on hydrogen bonding between peptide strands to hold the structure together (see p. 6, lines 6-11 of the specification). In a β-sheet structure, peptides are packed in an extended strand conformation which facilitates the display of the presenting group on the surface of the SAM and minimizes non-specific binding to the surface of the SAM (see Exhibit A, Keller *et al.*, *Supramolesular Science*, *2*:155 at p. 160, Col. 1, lines 9-11).

SAMs that have a charged presenting group are difficult to form because they resist close packing due to charge repulsion of the presenting groups. For example, a SAM made with a molecular species that had a C10 alkyl spacer and a carboxylic acid head group did not have the desired closely packed structure with the carboxylic acid groups displayed on the surface (see Exhibit A, Col. 1, p. 158, paragraph 1). The ordered structure of SAMs made from peptides is a result of hydrogen bonding between the peptide strands which are stronger than the hydrophobic forces that facilitate the packing of molecular species made with alkyl spacers. Therefore, SAMs made with peptide molecular species are expected to have an improved capacity to display charged presenting groups.

Both Wang *et al.* and Kumar *et al.* disclose molecular species that have alkyl or aryl spacer. Because Applicants' peptide molecular species are more easy to synthesize and have unique packing properties not found in the molecular species disclosed by Wang *et al.* and Kumar *et al.*, Applicants' method of manufacturing SAMs claimed in Claims 18 and 19, and Applicants' method of culturing cells claimed in Claim 20, are non-obvious over Wang *et al.* in view of Kumar *et al.* Therefore, Applicants respectfully request that the rejection be withdrawn.

CONCLUSION

In view of the above amendments and remarks, it is believed that all claims are in condition for allowance, and it is respectfully requested that the application be passed to issue. If the Examiner feels that a telephone conference would expedite prosecution of this case, the Examiner is invited to call the undersigned at (781) 861-6240.

Respectfully submitted,

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